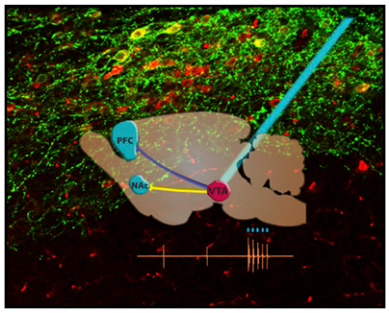
Dynamic and Diverse Roles of Dopamine

Neural circuits are dynamically regulated by a diverse class of secreted molecules known as neuromodulators, among which is dopamine, a molecule linked to disorders such as Parkinson's disease and schizophrenia and to reward-driven learning. This Select highlights several recently published papers that elucidate how dopamine neurons regulate circuits involved in depression-related behaviors, learning related to nutritional reward, and susceptibility to addiction.



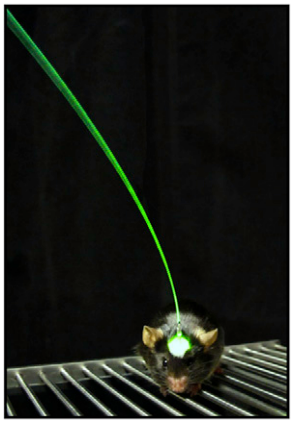
Optogenetic activation of midbrain dopamine neurons promotes susceptibility to severe social stress. Image courtesy of N. Friedman, V. Burnham, A. Friedman, J. Walsh, and M.-H. Han.

Defeating Depression

Mice often exhibit social avoidance following repeated attack by a larger mouse, a behavioral response known as social defeat stress that has been used as a model for depression-related behavior in humans. Chaudhury et al. (2013) now use optogenetic techniques to show that phasic firing of the dopamine neurons of the ventral tegmental area (VTA) promotes susceptibility to social defeat stress. Expression in the VTA neurons of a fluorescently tagged channelrhodopsin-2 allows these neurons to be selectively stimulated by pulses of light delivered through a cannula implanted in the skull. The authors report that phasic stimulation of the VTA dopamine neurons is sufficient to promote social avoidance following social defeat stress (the susceptible phenotype), and optogenetic stimulation of these neurons during the social interaction test instantly causes mice that had previously shown resistance to social defeat stress to exhibit social avoidance. VTA dopamine neurons that project to the nucleus accumbens (NAc), which have been implicated in reward and stress responses, have a higher firing rate after social defeat stress in susceptible mice, and stimulation of these neurons is sufficient to induce the social avoidance phenotype; conversely, inhibition of these neurons instantly induces the stress-resistant phenotype. In contrast, VTA dopamine neurons projecting to the medial prefrontal cortex (mPFC) have a decreased firing rate in mice susceptible to social defeat stress, and optogenetic inhibition of these neurons during the social interaction test induces the susceptible phenotype. These results confirm the proposed role of the VTA-NAc dopamine neurons in modulation of depression-related symptoms, and the rapid responses after optogenetic manipulation mirror the rapid antidepressant effects of the drug ketamine, pointing to a rapidly reversible signaling mechanism in the brain that might be manipulated to treat depression.

Chaudhury, D., et al. (2013). Nature 493, 532–536. Published online December 12, 2012. http://dx.doi.org/10.1038/nature11713.

Dialing Down Dopamine in Real Time



Optogenetic inhibition achieved by delivering light via optical fiber to a freely moving mouse expressing a microbial opsin gene. Image courtesy of I. Goshen and K. Deisseroth.

Whereas the study by Chaudhury et al. (2013) elucidates how subsets of neurons projecting from the VTA modulate susceptibility to severe stress in mice, a study by Tye et al. (2013) uses optogenetic techniques and electrophysiology to explore how VTA dopamine neurons control chronic mild stress-induced depression-related behaviors as well as downstream neural activity (measured in real time in the NAc). The manifestation of escape-related behaviors in response to stress has been used as a model of depression in rodents, with immobility in a rodent suspended by its tail being analogous to behavioral despair. Tye et al. (2013) show that optogenetically induced hyperpolarization of VTA dopamine neurons instantly abrogates struggling in mice subjected to a tail suspension test, and withdrawal of the hyperpolarization rapidly restores struggling behavior. They also use the technique to examine anhedonia, an inability to experience pleasure or lack of motivation to engage in a pleasurable activity, symptoms of depression in humans. The authors measure this through a sucrose preference test, in which licks on spouts delivering either water or a sucrose solution are counted in real time, with lack of preference for sucrose indicating anhedonia. Hyperpolarization of the VTA dopamine neurons causes a rapid and reversible drop in preference for sucrose. Furthermore, optogenetically induced phasic firing of the VTA dopamine neurons reverses the decline in escape-related behavior acquired during conditioning by chronic mild stress (CMS), confirming a causal link in activity of these neurons to a depression-like state. By measuring escape-related behavior during a forced swim test after CMS conditioning while simultaneously making electrophysiological recordings in the NAc, Tye et al. (2013) find that NAc neurons show phasic electrophysiologic responses to optogenetic stimulation in the VTA, responses that also correlate with escape-related actions. The neural representation of escape behavior in the NAc is altered by optogenetic activation of the VTA dopamine neurons, suggesting that control of depression symptoms may involve changes in neural circuitry mediated by dopamine neurons.

Tye, K., et al. (2013). Nature 493, 537–541. Published online December 12, 2012. http://dx.doi.org/10.1038/nature11740.

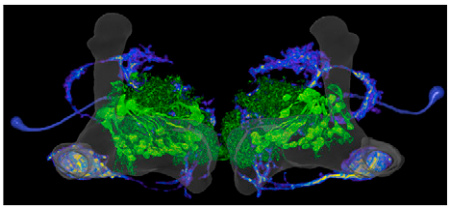
Cellular mechanism underlying enhanced synaptic plasticity in dopamine neurons through which adolescent social isolation may increase addiction vulnerability. Image courtesy of M. Grenadier and H. Morikawa.

Isolation Molds the Minds of Young Rats

The VTA dopamine neurons also promote learning of what environmental stimuli and behaviors are associated with rewards, a process implicated in drug addiction. In humans, social isolation alters the response to natural rewards (such as food) and to addictive drugs, and rodents have been used to model social isolation, with isolation during a critical period in early adolescence having the greatest (and irreversible) effects. Whitaker et al. (2013) show that social isolation of rats in early adolescence enhances the long-term potentiation (LTP) of NMDA-receptor-mediated glutamatergic transmission in the VTA dopamine neurons, promoting the acquisition of memories associated with addictive drugs. Social isolation of rats before single-day conditioning with amphetamine causes a more consistent and robust change in preference for an amphetamine-paired compartment compared to group-housed rats. The difference between the isolated and group-housed rats decreases with longer conditioning with amphetamine, showing that social isolation increases the rate of learning of stimuli associated with the drug. Mechanistically, social isolation during early adolescence increases the Ca^{2+} signal evoked in VTA dopamine neurons by metabotropic glutamatergic input, an effect that cannot be reversed by subsequent socialization. Ca^{2+} release is prompted by the intracellular messenger IP_3, and social isolation increases the sensitivity of the VTA neurons to IP_3, enhancing LTP. The results show that social deprivation during a critical period in early adolescence enhances synaptic plasticity of glutamatergic transmission in the VTA dopamine neurons and suggest how social deprivation in human adolescents might cause long-term susceptibility to drug addiction.

Whitaker, L., et al. (2013). Neuron 77, 335–345.

Neuromodulation of a Fly's Sweet Tooth



Octopamine reinforces *Drosophila* memory through rewarding (green) and motivating (blue) dopamine neurons. Image courtesy of W. Huetteroth and S. Waddell.

Although motivation and learning related to nutritional or drug reward are closely linked with the dopaminergic system in mammals, in insects, it is another neuromodulator, octopamine, that has been more frequently invoked as the reward signal. Now, Burke et al. (2012) dissect the neural circuit of appetitive memory formation in fruit flies and show that octopamine works through dopaminergic neurons in this process. A temperature-sensitive, reversible blockade of synaptic transmission from the octopamine neurons surprisingly fails to block appetitive memory of nutritious sucrose, suggesting the existence of another signal. These flies are unable to form an appetitive memory of arabinose, a sugar that is sweet but not nutritious, suggesting that octopamine might only represent sweet taste reinforcement, with nutrition providing an additional reinforcing signal in memory formation. Both the octopamine-dependent sweet signal and nutrition reinforcement turn out to converge on these downstream dopaminergic neurons. Short-term memory can be artificially induced through temperature-sensitive activation of octopamine neurons paired with presentation of an odor, and this process requires the dopamine neurons and the dopamine receptor. Octopamine acts on the β-adrenergic-like OAMB receptor in these rewarding dopamine neurons. Further experiments with flies mutant in a β-adrenergic like octopamine receptor, OCTβ2R, show that artificial learning through octopamine neuron activation also involves integration with another dopaminergic signal that is critical for appetitive motivation.

Burke et al. (2012). Nature 492, 433–437.

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